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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,317	12/20/1999	RANDOLPH NOELLE	012712-813	2231

7278 7590 03/30/2005

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/467,317	NOELLE, RANDOLPH	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/17/04; 4/27/04; 3/16/05. (Interview summary)

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 44, 46, 50, 52, 64-58, 60, 61, 63, 64, 66, 67, 69, 70, 72, 73, 75, 76, 78, 79, 81-86, 90-94 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: PTOL-90/communication

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09/467317

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER
1644	03282004

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Upon inquiry about the status of the instant application by applicant, it has been determined that the Office Action was completed and turned in for counting in November 2004, but was not mailed.

Further, it is noted that the examiner has signed and filled out the forms as of the current date, since the location of the originally submitted Office Action and accompanying papers have been misplaced.

The examiner apologizes for any inconvenience to the applicant in this matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 28, 2005

Continuation of Disposition of Claims: Claims pending in the application are 44,46,50,52,54-58,60,61,63,64,66,67,69,70,72,73,75,76,78,79,81-86 and 90-94.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 3/17/04, has been entered.

Applicant's amendment, filed 4/27/04, has been entered.
Claims 1-43, 45, 47-49, 51, 53, 59, 62, 65, 68, 71, 74, 77, 80 and 87-89 have been canceled.
Claims 91-94 have been added.

Claims 44, 46, 50, 52, 54-58, 60, 61, 63, 64, 66, 67, 69, 70, 72, 73, 75, 76, 78, 79, 81-86 and 90-94 are pending.

Applicant's First and Second Responses to Office Communication under 37 CFR 1.105, filed 8/9/04 and 8/11/04, respectively are acknowledged.

2. Applicant's provision of a substitute specification filed on 3/17/04 is acknowledged

3.The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The following is noted with regards to the holding of the Board of Patent Appeals and Interferences with respect to the enablement of chimeric antibodies encompassed by the disclosure of priority application USSN 08/742,480.

See On Requests For Clarification And For Reconsideration of Judgment On Preliminary Motions, mailed 2/21/03, Before the Board of Patent Appeals and Interferences, Patent Interference No. 104,724.

In parent application USSN 08/742,480, the Board of Patent Appeals and Interferences found that:

"Given the failure to substantiate a disclosed method of obtaining chimeric monoclonal antibodies by "standard techniques," the preponderance of the evidence persuades us that the amount of experimentation required to make them by any techniques would have been "undue". Accordingly, we hold that Noelle's specification does not provide an enabling disclosure of chimeric monoclonal antibodies that bind to the same antigen as does the antibody produced by MR1." See page 18.

It is noted that the Board did not take it upon itself to mine the record for evidence in support of one party or the other. See page 17, paragraph 1.

The following art provides for the enablement of chimeric antibodies to one of ordinary skill in the art at the time the invention was made, that is, 1992 (the filing date of USSN 07/835,799), which is the earliest priority date relied upon the instant application and USSN 08/732,480.

Morrison et al. (U.S. Patent No. 5,807,715), which has a U.S. priority date of 1984, teach the production of chimeric antibodies.

Neurberger et al. (U.S. Patent No. 6,808,901), which has U.S. priority date of 1986, teach the production of chimeric antibodies.

Winter et al. (U.S. Patent No. 5,225,539), which has a priority date of 1986, teach the production of CDR-grafted antibodies, which, in turn, was an advancement in the antibody art over chimeric antibodies.

Queen et al. (U.S. Patent No. 5,530,101), which has a filing date of 1990 and a priority date of 1988, teaches the production of humanized antibodies, which, in turn, was an advancement in the antibody art over chimeric and CDR-grafted antibodies.

With respect to chimeric antibodies as it relates to antibodies to CD40L, the following patents also rely upon art recognized methods of generating chimeric antibodies to one of ordinary skill in the art at the time the invention was made.

In describing humanized antibodies specific for CD40L (gp39), Black et al. (U.S. Patent No. 6,506,383) recognized chimeric antibodies in the Background of the Invention. For example, see column 6, paragraph 2.

Similarly, Noelle et al. (U.S. Patent No. 6,375,950) recognized the approach of minimizing immunogenicity of therapeutic antibodies by the production of chimeric antibodies as known and practiced by the ordinary artisan at the time the invention was made. For example, see column 6, paragraph 2.

With respect to the concerns of the Board of Interferences concerning the need to first obtain nucleic acids encoding antibodies, Morrison et al. (Advances in Immunology 44: 65-92, 1989) notes that one does not need to determine the amino acid sequence of a rearranged V region before cloning by relying upon art known immunoglobulin probes in their discussion on cloning and manipulating antibody genes (see entire document, including page 73, paragraph 1).

Therefore, chimeric and humanized antibodies are deemed enabled at the time the invention was made, which is the filing date of the earliest priority application USSN 07/835,799, filed 2/14/92.

5. The previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter, with respect to the recitation of "A method for inhibiting ... to a protein specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC No. HB 11048" has been withdrawn in view of applicant's amended claim 48, filed 6/9/03.

6. The previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter, with respect to the recitation of "a 39 kD protein located on T helper cell membranes" has been withdrawn in view of applicant's amended claims.

7. The previous rejection under 35 U.S.C. § 112, first paragraph, written description / new matter with respect to "A method for inhibiting a humoral immune response ... " has been withdrawn given applicant's amended claims.

8. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 83-86 and 90-94 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

Newly submitted claims 83-86 and 90-94 recite the targeted "antigen" by certain characteristics.

With respect to a previous claimed recitation drawn to "a 39 kD protein located on T helper cell membranes"; applicant has asserted that the scope of claimed supported by the application as filed (e.g. page 2, lines 27 - page 3, line 4 of the instant specification) as well as the functional properties of a CD40CR protein, including its ability to bind CD40 B-cell antigen and to stimulate B cell cycle entry, proliferation and differentiation", satisfies the written description of a CD40CR protein.

In addition, applicant had submitted that at the time of filing of the instant application, CD40CR had been described in several species, including Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992) and Spriggs et al. (J. Exp. Med 176: 1543-1550 (1992).

It was noted that neither Hollenbaugh et al. (EMBO J 11: 4313-4321, 1992) nor Spriggs et al. (J. Exp. Med 176: 1543-1550 (1992) were disclosed in the application as filed.

Applicant's assertions that the art following a review of the disclosure of the instant application would conclude that the applicant was in possession of the necessary common attributes possessed by antibodies that bind to the claimed CD40CR "antigen", currently recited is not consistent with the requirements under 35 USC 112, first paragraph, written description as well as the holdings of the Federal Circuit in addressing the written description of CD40CR in parent application USSN 07/742,480. See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004).

There is insufficient written description encompassing the claimed Aantigen≅ specificity because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of the claimed "antigen" (i.e. "CD40CR") are not set forth in the specification as filed, commensurate in scope with the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is relying upon certain biological activities and the disclosure of the limited representative species of a mouse CD40CR antigen (e.g. see Sections 6.2.3 and 6.2.4 as well as Figures 4- 6) to support an entire genus of CD40CR antigens as it reads on mammalian and human CD40CR antigens. The instant invention encompasses any CD40CR antigen as a target of the instant methods, yet the instant specification does not provide sufficient written description as to the structural features of said CD40CR antigen and the correlation between the chemical structure and the function of the genus of CD40CR antigens. Applicant appears to rely upon the disclosure of a limited example of a mouse CD40CR antigen.

While the specification discloses a starting point for screening or testing for molecules that have the characteristics of a CD40CR antigen (e.g. 39 kD protein on helper T cells membranes, which binds to CD40 B cell antigen and stimulates B cell cycle entry); the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such antigens broadly encompassed by the claimed invention and it does not identify a sufficient number of representative members of such mammalian CD40CR antigens (e.g. human CD40 ligand). The application does little more than describe the desired function of the claimed genus of CD40CR antigens broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

While Section 7 of the instant specification discloses binding of CD40Ig to human T cell lines, there is no isolation nor written description of the human CD40CR antigen.

Furthermore, there is insufficient written description of the genus of CD40CR antigens, including as it reads on mammalian CD40CR antigens as well as human CD40CR antigen.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Further, Skolnick et al. (Trends in Biotech., 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse CD40CR disclosed as filed does not appear to provide sufficient written description of a genus of distinct molecules of ACD40CR(s), encompassed by the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Further, it is noted that priority application USSN 08/742,480 was party to an Interference with the United Stated Patent and Trademark Office Board of Patent Appeals and Interferences (Interference No. 104,415). See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004).

With respect to the disclosure of antibodies that bind a genus of CD40CR antigens, including human CD40CR; the Court affirmed the decision by the Board supported by substantial evidence and the law which held that the USSN 08/742,480 application lacked written description for the genus of CD40CR antigens, including human CD40CR antigen.

Given the state of the art in the early 1990's described by the expert witnesses and evidence, the Court also affirmed the decision by the Board by finding that one skilled in the art would have lacked a reasonable likelihood of success in isolating human CD40CR antigen given mouse CD40CR antigen, including consideration of Noelle's reliance on various screening methods disclosed in the specification.

Applicant has not disclosed "a fully characterized antigen" as it reads on human CD40CR antigen or the genus of CD40CR antigens encompassed by the claims.

In the absence of structural characteristics that are shared by members of the genus of ACD40CR antigens; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant's reliance upon reciting CD40CR antigen, including mammalian and human CD40CR antigens, by certain characteristics has not found been persuasive in obviating the written description rejection under 35 USC 112, first paragraph, for the scope of CD40CR antigens encompassed by the claimed invention.

9. Claims 83-86 and 90-94 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for "the protein specifically recognized by monoclonal antibody MR1 produced by the hybridoma having ATCC Accession No. HB 11048" as claimed and disclosed in the instant specification, does not reasonably provide enablement for
any "antigen having the characteristics recited in instant claims 83-86 (a)-(c)".
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification only discloses that the mouse CD40CR antigen as claimed, that is, Athe protein specifically recognized by monoclonal antibody MR1 produced by the hybridoma having ATCC Accession No. HB 11048"

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the genus of CD40CR antigens as the target specificity of the claimed methods.
While the instant disclosure and the claims provide a source (e.g. activated but not resting T cells) and a comparison to a referenced molecular weight, claiming biochemical molecules by such characteristics fails to enable what that CD40CR antigen is and what it is made up of.
Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.
The specification does not describe nor enable any ACD40CR antigen" broadly encompassed in the claimed methods.

Applicant is relying upon certain biological activities and the disclosure of the limited representative species of a mouse CD40CR antigen (e.g. see Sections 6.2.3 and 6.2.4 as well as Figures 4- 6 of the instant specification) to support an entire genus of CD40CR antigen as it reads on mammalian and human CD40CR antigens. The instant invention encompasses any CD40CR antigen as a target of the instant methods, yet the instant specification does not provide guidance on how to make and how to use the essential structural features of said genus of CD40CR antigens and the correlation between the chemical structure and the function of the genus of CD40CR antigens. Applicant appears to rely upon the disclosure of a limited example of a mouse CD40CR antigen.

While the specification discloses a starting point for screening or testing for molecules that have the characteristics of a CD40CR antigen (e.g. 39 kD protein on helper T cells membranes, which binds to CD40 B cell antigen and stimulates B cell cycle entry); the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery for such antigens broadly encompassed by the claimed invention and it does not identify a sufficient number of representative members of such antigens (e.g. human CD40 ligand). The application does little more than describe the desired function of the claimed genus of CD40CR antigens broadly encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would be able to make and use the scope of CD40CR antigen specificities broadly encompassed by the claimed invention.

While Section 7 of the instant specification discloses binding of CD40Ig to human T cell lines, there is no isolation of the human CD40CR antigen as well as a sufficient number of species to satisfy the enablement of the genus of mammalian CD40CRs encompassed by the claimed invention.

Furthermore, there is insufficient isolation of the genus of CD40CR antigens, including as it reads on mammalian as well as human CD40CR antigen.

The specification describes methods for screening for CD40CR antigens that possess certain desired characteristics and identifies the mouse CD40CR antigen as well as the expectation that other mammalian species similarly express the CD40CR. However, this description without more precise guidelines amount to little more that a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention as broadly encompassed by the claimed invention.

Further, Skolnick et al. (Trends in Biotech 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse CD40CR disclosed as filed does not appear to provide sufficient written description of a genus of distinct molecules of ACD40CR(s), encompassed by the claimed invention.

Further, it is noted that parent application USSN 08/742,480 was party to an Interference from the United Stated Patent and Trademark Office Board of Patent Appeals and Interferences (Interference No. 104,415). See Noelle v. Lederman, 69 USPQ2d 1508 (CAFC 2004).

With respect to the disclosure of antibodies that bind a genus of CD40CR antigens, including human CD40CR; the Court affirmed the decision by the Board supported by substantial evidence and the law which held that the USSN 08/742,480 application lacked written description for the genus of CD40CR antigens, including human CD40CR antigen (see Decision, including pages 1508-1509, 1516-1517)

Given the state of the art in the early 1990's described by the expert witnesses and evidence, the Court also affirmed the decision by the Board by finding that one skilled in the art would have lacked a reasonable likelihood of success in isolating human CD40CR antigen given mouse CD40CR antigen, including consideration of Noelle's reliance on various screening methods disclosed in the specification (see Decision, including pages 1516-1517).

Applicant has not disclosed "a fully characterized antigen" as it reads on human CD40CR antigen or the genus of CD40CR antigens encompassed by the claims.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere isolation of a single protein and, in turn, predicting structural elements (e.g. amino acid or encoding nucleic acid sequences) to provide for a genus of CD40CR antigens that have the appropriate structural and functional characteristics of this genus of molecules is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the absence of sufficient guidance and direction to the structural and functional analysis of a sufficient number of species, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use the genus of mammalian "CD40CR antigens" other than the particular mouse CD40CR antigen identified by the MR1 monoclonal antibody.

10. Claims 67 and 69-70 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 67 and 69-70 are drawn to "human antibody comprising a binding fragment of monoclonal MR1".

Given that the claimed antibody MR1 is a hamster-derived antibody, the binding fragment of the MR1 antibody is hamster and not human.

The claims are not drawn to recombinant antibodies which are modifications of the hamster-derived MR1 antibody.
Rather, the claims are drawn to fully human antibody fragments of this hamster-derived MR1 antibody.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using human antigen binding fragments from a hamster-derived antibody, while providing or maintaining the claimed activity would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

11. Claims 57-58 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for Ainhibiting immunoglobulin production or activation of B cells in a mouse" with antibodies that specifically bind to a protein specifically recognized by the MR1 antibody,
does not reasonably provide enablement for
"inhibiting immunoglobulin production or activation of B cells in any animal or human".
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental observations accurately reflects the relative ability of antibodies that bind mouse CD40CR antigen (i.e. mouse CD40L) can inhibit immunoglobulin production or B cell activation in any non-mouse animal, including humans.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not teach how to extrapolate data obtained from in vitro and in vivo observations with targeting a mouse protein to inhibit immunoglobulin production or B cell activation to the development of effective in vivo inhibition of immunoglobulin production or B cell activation in any non-mouse animal or human. Given the mouse specificity of the MR1 antibody specificity, the skilled artisan would not have predicted that such anti-mouse antibodies would inhibit immune responses in an animal species other than mouse.

In view of the lack of predictability of the art to which the invention pertains the lack of established therapeutic or in vivo protocols for effective antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting immunoglobulin production and B cell activation in non-mouse animals.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(f) or (g) prior art under 35 U.S.C. § 103(a).

14. Claims 83-86 and 91-94 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lederman et al. (U.S. Patent No. 5,993,816) (see entire document).

Lederman et al. teach methods of inhibiting humoral immune responses, including B cell activation and immunoglobulin production as well as autoimmunity by 5c8-specific antibodies (e.g., see Background of the Invention, columns 10-11, and Example 7 on columns 23-27), including antibody fragments, chimeric, humanized and human antibodies as well as antibody conjugates (columns 6-8) (also, see Claims). The 5c8 specificity is the equivalent of the human CD40 ligand or CD40CR antigen, as encompassed and intended by the instant claims. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit humoral immune responses, B cell activation and immunoglobulin production as well as autoimmunity by 5c8-specific antibodies.

15. Claims 44, 46, 50, 52, 54, 57, 83-86 and 90-94 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 5,993,816) in view of Armitage et al. (U.S. Patent No. 5,961,974) essentially for the reasons of record.

Lederman et al. teach methods of inhibiting humoral immune responses, including B cell activation and immunoglobulin production as well as autoimmunity by helper T cell-specific antibodies, including the 5c8-specific antibodies (e.g., see Background of the Invention, columns 10-11, and Example 7 on columns 23-27), including antibody fragments, chimeric, humanized and human antibodies as well as antibody conjugates (columns 6-8) (also, see Claims). The 5c8 specificity is the equivalent of the human CD40 ligand or CD40CR, as recited in the instant claims.

Lederman et al. differs from the claimed methods by not disclosing the protein specifically recognized by the MR1 antibody which binds the mouse CD40 ligand (CD40L).

Armitage et al. teach the mouse and human CD40L on T cells, wherein CD40L is involved in T - B cell interactions, which are associated with B cell proliferation and differentiation resulting in immunoglobulin secretion (See entire document, including Detailed Description of the Invention and Examples 1-13). Armitage et al. teach the use of antagonists of CD40:CD40L interactions which prevent CD40L binding to CD40 sites on B cells and other target cells, which can be used in therapeutic modalities (see Detailed Description of the Invention) (e.g. columns 10-11, including overlapping paragraph, columns 14-17; column 21)

Given the ability of helper T cell 5C8-/CD40L-specific antibodies, as taught by Lederman et al. OR the ability of various CD40 antagonists, as taught by Armitage et al. to inhibit various immune responses, including T helper cell-mediated immune responses, including humoral responses; one of ordinary skill in the art at the time the invention was made would have been motivated to generate antibody antagonists, including antibody fragments, chimeric, humanized, human antibodies as well as antibody conjugates, as known by the ordinary artisan and taught by Lederman et al. to the mouse and human CD40L taught by Armitage et al. to similarly target T helper cells in order to inhibit humoral responses, B cell proliferation and immunoglobulin production.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 55-56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 5,993,816) in view of Armitage et al. (U.S. Patent No. 5,961,974)
as applied to claims 44, 46, 50, 52, 54, 57, 83-86 and 90-94 above and further in view of
the art known use of antibody conjugates in inhibiting immune responses by the ordinary artisan at the time the invention was made, as evidenced by Ultee et al. (U.S. Patent No. 4,937,183) essentially for the reasons of record.

Lederman et al. and Lederman et al. in view of Armitage et al. are taught above and differ from the claimed methods by not disclosing all of the well known antibody conjugates and therapeutic agents recited in claims 55-56.

A wide variety of antibody conjugates for inhibiting immune responses were well known and practiced by the ordinary artisan at the time the invention was made, including those recited in claim 55, as evidenced by Ultee et al. (See entire document, including Section 5.2, particularly columns 7-8, overlapping paragraph, Sections 5.3, 5.4, 5.5).

Given the well known use of a variety of antibody conjugates employed in therapeutic modalities to inhibit immune responses, it would have been obvious to one of ordinary skill in the art to conjugate either human or mouse CD40L-specific antibodies to inhibit humoral immune responses, including the inhibition of B cell activation and immunoglobulin production, as taught by Lederman et al. or Lederman et al. in view of Armitage et al. as taught above, at the time the invention was made. The various conjugates were well known to provide additional immunosuppressant properties for therapeutic antibodies that target cells of interest at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims which employ the MR1 antibody produced by the hybridoma having the ATCC Accession No. HB 11048 appear to be free of the prior art. Due to high polymorphism of antibodies, the MR1 antibody produced by the ATCC Accession No. HB 11048 is deemed structurally distinct on the primary amino acid basis and therefore free from the prior art.

Claims 60, 61, 63, 64, 66, 72, 73, 75, 78, 79, 81 and 82 are deemed allowable.

For examination purposes, it is noted that the recitation of "fragments" in claims 66, 72, 73, 75, 76, 78, 79, 81 and 82 is interpreted to mean "fragments of the MR1 antibody" and not "fragments of the MR1 antibody as produced by the hybridoma having ATCC Accession No. HB 11048.
As a general rule, hybridomas produce entire antibodies and do not produce fragments of antibodies.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

571.273.8300

The fax number for the organization where this application or proceeding is assigned is ~~703-872-9306.~~

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 12, 2004

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3/28/05